The National Toxicology Program Processes in Relation to the Authoritative Bodies Mechanism in Proposition 65 June 2003

INTRODUCTION

The Safe Drinking Water and Toxic Enforcement Act of 1986, better known as "Proposition 65," requires the listing of chemicals known to the State of California to cause cancer or reproductive toxicity. One of the mechanisms by which a chemical may be added to the Proposition 65 list is if an "authoritative body" formally identifies a chemical as causing cancer or reproductive toxicity (Health and Safety Code Section 25249.8(b)). The National Toxicology Program (NTP) is an authoritative body for purposes of formally identifying chemicals known to the State to cause cancer (Title 22, California Code of Regulations, Section 12306(m)(3)). As such, various documents generated by NTP are examined by the Office of Environmental Health Hazard Assessment (OEHHA) to determine whether or not they may serve as the basis for an "authoritative bodies" listing of a chemical under Proposition 65. In fact, OEHHA has added numerous chemicals to the Proposition 65 list based on NTP Technical Reports and the NTP Report on Carcinogens (RoC). However, some parties have questioned whether the NTP Technical Report Series satisfies the authoritative body regulatory criteria to serve as the basis for listing a chemical under Proposition 65. More specifically, some parties have argued that the NTP Technical Report Series is linked to publication of the RoC and that issuance of an NTP Technical Report is only a preliminary step toward compilation and publication of the RoC. This paper examines that issue and concludes that NTP Technical Report Series does satisfy the "formality" component of the controlling regulation for authoritative body listings.[1]

The determination whether a particular document generated by an authoritative body satisfies the requirements in Title 22, California Code of Regulations, Section 12306 (Section 12306) such that it formally identifies a chemical as causing cancer or reproductive toxicity is specifically delegated to the lead agency (OEHHA) (Section 12306(c)). The ultimate determination whether a chemical meets the sufficiency of the evidence standards specified in Section 12306(e) or (g) for listing under Proposition 65 must proceed on a case-by-case basis. However, standardized approaches and protocols utilized uniformly for certain documents issued periodically by various authoritative bodies make it possible to analyze these "standardized documents" categorically against the threshold "formality requirements" set out in Section 12306(d). As the detailed analysis below indicates, OEHHA has reviewed the NTP Technical Report Series and determined that they, as well as the RoC, satisfy the formality requirements in Section 12306(d).

[1] "Formality requirements" is used throughout to refer to those provisions of the controlling regulation addressing the nature and status of a document, as opposed to those dealing with the particular finding or conclusions within the document regarding the carcinogenicity of the given chemical.

THE REGULATORY STANDARD:

This section sets out a two-part standard for determining whether a chemical has been formally identified as causing cancer or reproductive toxicity. The first part, set out in Section 12306(d) and (d)(1), focuses on the *identification* aspect of the document. It provides three alternative means of satisfying this aspect of the authoritative bodies listing mechanism. It reads as follows:

"(d) For purposes of this section a chemical is "formally identified" by an authoritative body when the lead agency determines that:
(1) the chemical has been included on a list of chemicals causing cancer or reproductive toxicity issued by the authoritative body; or (2) is the subject of a report which is published by the authoritative body and which concludes that the chemical causes cancer or reproductive toxicity; or (3) has otherwise been identified as causing cancer or reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action; and" (bracketed numbers added for clarity).

The second part of Section 12306(d), set out in paragraph (2), addresses the *formality* aspect of the document that serves as the potential basis for the listing of a chemical under Proposition 65. It provides six separate alternative means of satisfying this element of the authoritative bodies listing mechanism. It reads as follows:

"(2) the list, report, or document specifically and accurately identifies the chemical, and has been:
(A) Reviewed by an advisory committee in a public meeting, if a public meeting is required, or
(B) Made subject to public review and comment prior to its issuance, or
(C) Published by the authoritative body in a publication, such as, but not limited to, the federal register for an authoritative body which is a federal agency, or
(D) Signed, where required, by the chief administrative officer of the authoritative body or a designee, or
(E) Adopted as a final rule by the authoritative body, or
(F) Otherwise set forth in an official document utilized by the authoritative body for regulatory purposes."

These two components form the entirety of the framework for regulatory analysis to determine whether a given document satisfies the "formally identified" aspect of a potential authoritative body listing. Therefore, it is against this standard that we examine the Technical Report Series and the RoC documents published by NTP. It should be noted at this point that if a document satisfies the requirements of Section 12306, OEHHA is under a mandatory duty to proceed with the listing of that chemical under Proposition 65.

National Toxicology Program:

The Department of Health and Human Services (DHHS) established the NTP in 1978 to accomplish myriad objectives. These include: coordinating toxicological testing programs within DHHS; strengthening the science base in technology; developing and validating improved testing methods; and providing information about potentially toxic chemicals to health regulatory and research agencies, the scientific and medical communities, and the public (National Toxicology Program, 2001, NTP Current Directions and Evolving Strategies available at http://ntp-server.niehs.nih.gov/Main_Pages/PUBS/NTP2001CurrDir.pdf) ("NTP 2001," p. 2). These related, but distinct, goals and functions of NTP are reflected in: the legislative mandates governing NTP activities; the structure and organization of NTP; and in the variety of work it performs and documents it generates. A very brief examination of each of these issues is in order.

NTP Legislative Authorities and Mandates:

The two principal activities of the NTP examined in this paper are the performance of studies by NTP leading to the issuance of NTP Technical Reports and the publication of the RoC. The legislative underpinnings for these two distinct activities are set out separately in Title 42, United States Code, Section 241 (Section 241). Section 241 requires the Secretary of DHHS to carry out various duties and then confers certain authority on the Secretary to allow for the carrying out of these duties. More specifically, this provision, among other things, requires the Secretary of DHHS to "conduct…studies and testing of substances for carcinogenicity, teratogenicity, mutagenicity, and other harmful biological effects" (Section 241(b)(1)). It is under this provision (Section 241(b)(1)) that NTP conducts its studies and testing of agents that may cause cancer, culminating in the publication of the NTP Technical Reports. NTP issues the RoC under a separate statutory mandate.

The Secretary of DHHS publishes the RoC pursuant to Section 241(b)(4). That provisions states as follows:

"The Secretary [of DHHS] shall publish a biennial report which contains—
(A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;"

Quite simply, the statutory mandates, scope, and functions of the NTP Technical Reports and the publication of the NTP RoC are distinct from each other. The former consists of the "first-hand bench science" evaluation of a chemical performed by NTP itself. In addition, the NTP Technical Reports are published for all chemicals tested regardless of the outcome of the testing or the degree of human exposure, if any, to the chemical. The RoC, by way of contrast, reflects the distillation and compilation of all relevant data for chemical agents regardless of the source of that data. However, it includes **only** those chemicals that have positive carcinogenic findings **and** for which there is a significant number of people exposed in the United States. That is, even a potent carcinogen that was the subject of testing by NTP and included in an NTP Technical Report *cannot* be included in the RoC unless a significant number of people in the United States

are exposed to the chemical. By way of contrast, there is no parallel provision in Section 241(b)(1) governing the scope of the NTP Technical Reports. When NTP issues its Technical Reports it is operating pursuant to a regulatory regime separate and apart of the publication of the RoC and vice versa. There is no statutory "linkage" of these distinct regulatory efforts.

NTP Structure and Organization:

NTP has both a Policy Oversight organizational hierarchy and an External Science Oversight and Peer Review organizational structure. The critical component for purposes of Proposition 65 is the "External Science Oversight and Peer Review" organizational structure. This scheme consists of: the NTP Board of Scientific Counselors (the Board); the NTP Technical Reports Review Subcommittee of the Board; RoC Subcommittee of the Board; and the Advisory Committee on Alternative Toxicological Methods (NTP 2001, p. 4). Again, the organizational structure of NTP, with separate committees for the NTP Technical Reports and the RoC, reflects the separate nature of these two report series. Yet again, the distinct nature of the NTP Technical Reports and the RoC is also reflected in NTP's description of the process by which chemicals come to be included in these two report series. The processes leading to the publication of these reports, as described by NTP, are outlined below.

Technical Report Preparation:

NTP accepts nominations of candidate chemicals proposed for evaluation. These nominations are then subject to review by the Interagency Committee for Evaluation and Coordination. This step is followed by public review. Next comes evaluation by the NTP Board of Scientific Counselors at a public meeting. After this, the NTP Executive Committee engages in review and selection of the chemicals that will be tested by NTP. NTP then designs and initiates studies based on resources, priorities, and knowledge gaps. Ultimately, these study results are published in NTP Technical Reports (NTP 2001, p. 5).

NTP further describes this process as follows: "Longer-term studies, generally two-year rodent studies, are published as NTP Technical Reports and may also be published in peer-reviewed scientific journals. Both types of studies [short term and long term] undergo peer review prior to publication. The NTP Technical Reports Review Subcommittee evaluates the Technical Reports from carcinogenicity and toxicity studies in open public meetings" (NTP 2001, p. 6). What is critical about this functional and narrative description by NTP of the processes it employs related to the evaluation of chemicals and the publication of the NTP Technical Reports is the complete absence of any mention, let alone tie-in or linkage, to the NTP RoC. Once more, this is because they are distinct tasks performed by NTP pursuant to different mandates for different purposes. Accordingly, it is not surprising to learn that the RoC is nowhere mentioned by NTP as something that is related to or "follows" the publication of the NTP Technical Reports. In other words, the publication of an NTP Technical Report is certainly <u>not</u> preparatory to the RoC development process.

RoC Preparation:

NTP describes the RoC development process as follows: "Specific criteria are used to assess whether a nomination should be included in the RoC. The review of nominations for listing in or delisting from the RoC involves a multi-phased peer-review process with participation by representatives from federal agencies [examples omitted]. The NTP Director evaluates all review group recommendations, public comments, and other information in developing his recommendation to the Secretary of DHHS" (NTP 20001, p. 20). Yet again, there is an absence or any reference to a relationship between the RoC and the NTP Technical Reports. In simple terms, the publication of an evaluation of a chemical performed by NTP in a Technical Report is not a step on the road to inclusion of this chemical in the RoC. One would not "wait" then for the inclusion of the evaluation of a chemical that was subject to evaluation in an NTP Technical Report to be "included" or "finalized" in the NTP RoC. This is because there is no basis for the premise that a programmatic or linear relationship between the two documents exists. Some chemicals may be nominated for inclusion in the RoC after the publication of an NTP Technical Report with positive findings, and if there is a significant number of people in the United States exposed. If both of these conditions are met, the chemical may become listed in the RoC. However, there is no required consideration of chemicals with positive findings in NTP Technical Reports for nomination or inclusion in the RoC.

Documents Generated by NTP:

The NTP Technical Reports use a five-tiered hierarchy for evaluating the level of evidence of carcinogenic activity of the chemicals evaluated. These are in descending order: clear evidence, some evidence, equivocal evidence, no evidence, or inadequate study in individual experiments (e.g., male mice, female mice, male rats, and female rats). By way of comparison, the RoC uses the formulation set out above from Section 241(b)(4). That is, the RoC, consisting of only those chemicals for which there are positive findings, evaluates all of the relevant data related to the chemical in question. This frequently includes information from the International Agency for Research on Cancer (IARC). The RoC ultimately rates the chemical as either "known to be a human carcinogen" or "reasonably anticipated to be a human carcinogen." Unlike the NTP Technical Reports, there is no possibility of chemicals with a lower quality of positive evidence than indicated by either of these two conclusions being included in the RoC. The disparate nature of the classification schemes and attendant differences in terminology again reflect the distinct nature of the NTP Technical Reports and the RoC.

APPLICATION OF SECTION 12306(d) TO THE NTP TECHNICAL REPORTS SERIES:

As cited above, Section 12306(d)(1) specifies that a chemical has been "formally identified" when it "is the subject of a report which is published by the body and which concludes that the chemical causes cancer or reproductive toxicity." Again, the above quoted portion of the regulation is designed precisely to allow certain types of reports, if they meet the specified criteria, to qualify as a formal identification. If inclusion on a more formal or more inclusive "list" or "classification" were the only basis for a formal identification, this language would have no function. OEHHA has determined that the current content and structure of the NTP Technical

Report Series satisfy this criterion of the formal identification regulation. NTP Technical Reports with findings of "clear evidence" of carcinogenic activity in at least one experiment are examined to determine whether listing via the authoritative bodies mechanism is required. In such cases, OEHHA examines the Technical Report to determine whether the technical criteria in Section 12306(e) are met. Thus, the evidence is deemed "sufficient" for listing via this mechanism if there is "an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset" (Section 12306(e)).

In addition to satisfying one alternative means set out in Section 12306(d)(1), the NTP Technical Report Series satisfy at least two of the six alternative means of satisfying the "formality" element set out in Section 12306(d)(2). As discussed above, all of the NTP Technical Reports undergo peer review in a public meeting. This satisfies Section 12306(d)(2)(A). In addition, the NTP Technical Reports undergo public review and comment prior to issuance. This satisfies Section 12306(d)(2)(B). In the case of the NTP Technical Report Series, at least two of the six alternative grounds for establishing formality are met. In addition, upon publication of the technical reports by NTP, they also satisfy Section 12306(d)(2)(C). Again, any one of these alternative bases is sufficient to satisfy the "formality" provision of Section 12306(d)(2).

Other Relevant Information:

In addition to meeting the regulatory criteria for an authoritative bodies listing, the NTP Technical Reports were specifically considered by the Carcinogen Identification Committee (CIC) and were affirmatively retained as "authoritative" — even though such action was not required by the CIC. More specifically, on September 25, 1998, the CIC met to revisit the five entities it had previously designated as authoritative for purposes of identifying chemicals known to the State to cause cancer. NTP was among those five bodies. There was a recommendation made by a member of the public that NTP be designated as authoritative only as to identification of chemicals causing cancer in the RoC (9/25/98 CIC Meeting Transcript, p. 77).

This recommendation prompted significant discussion among members of the CIC, OEHHA representatives, and the public commenter (9/25/98 CIC Meeting Transcript, pp. 78-87, p. 93). The CIC specifically considered and rejected the recommendation that NTP should not "be considered an authoritative body when it draws conclusions in an individual study report, such as in NTP bioassays" (9/25/98 CIC Meeting Transcript, p. 78, p. 93). The CIC determination in this regard is consistent with OEHHA's view that NTP Technical Reports may properly serve as the basis for formal identification of a chemical as known to the State to cause cancer under the authoritative bodies listing mechanism of Proposition 65.

CONCLUSION:

NTP has been designated without limitation or qualification by the CIC as an authoritative body for the purposes of identifying chemicals as known to the State to cause cancer. The NTP Technical Reports may on a case-by-case basis satisfy the "formal identification" provisions of Section 12306(d). Accordingly, OEHHA will review NTP Technical Reports as they are issued

to determine whether the NTP concludes that the chemical tested causes cancer and whether the evidence set out by NTP satisfies the scientific criteria for listing specified in Section 12306(e). The NTP RoC also satisfies the formal identification provisions of Section 12306(d). Therefore, OEHHA will continue to review the RoC listings of chemicals to see whether they satisfy the other pertinent provisions of Section 12306.